REFLUDAN - lepirudin powder
Bayer HealthCare Pharmaceuticals Inc.

Rx Only

DESCRIPTION

REFLUDAN [lepirudin (rDNA) for injection] is a highly specific direct inhibitor of thrombin. Lepirudin, (chemical designation: [Leu^1, Thr^2]-63-desulfohirudin) is a recombinant hirudin derived from yeast cells. The polypeptide composed of 65 amino acids has a molecular weight of 6979.5 daltons. Natural hirudin is produced in trace amounts as a family of highly homologous isopolypeptides by the leech *Hirudo medicinalis*. The biosynthetic molecule (lepirudin) is identical to natural hirudin except for substitution of leucine for isoleucine at the N-terminal end of the molecule and the absence of a sulfate group on the tyrosine at position 63.
The activity of lepirudin is measured in a chromogenic assay. One antithrombin unit (ATU) is the amount of lepirudin that neutralizes one unit of World Health Organization preparation 89/588 of thrombin. The specific activity of lepirudin is approximately 16,000 ATU/mg. Its mode of action is independent of antithrombin III. Platelet factor 4 does not inhibit lepirudin. One molecule of lepirudin binds to one molecule of thrombin and thereby blocks the thrombogenic activity of thrombin. As a result, all thrombin-dependent coagulation assays are affected, eg, activated partial thromboplastin time (aPTT) and prothrombin time (PT /INR) values increase in a dose-dependent fashion (*Roethig 1991*).
REFLUDAN is supplied as a sterile, white, freeze-dried powder for injection or infusion and is freely soluble in Sterile Water for Injection USP or 0.9% Sodium Chloride Injection USP.
Each vial of REFLUDAN contains 50 mg lepirudin. Other ingredients are 40 mg mannitol and sodium hydroxide for adjustment of pH to approximately 7.

CLINICAL PHARMACOLOGY

Pharmacokinetic Properties

The pharmacokinetic properties of lepirudin following intravenous administration are well described by a two-compartment model. Distribution is essentially confined to extracellular fluids and is characterized by an initial half-life of approximately 10 minutes. Elimination follows a first-order process and is characterized by a terminal half-life of about 1.3 hours in young healthy volunteers. As the intravenous dose is increased over the range of 0.1 to 0.4 mg/kg, the maximum plasma concentration and the area-under-the-curve increase proportionally.
Lepirudin is thought to be metabolized by release of amino acids via catabolic hydrolysis of the parent drug. However, conclusive data are not available. About 48% of the administration dose is excreted in the urine which consists of unchanged drug (35%) and other fragments of the parent drug.
The systemic clearance of lepirudin is proportional to the glomerular filtration rate or creatinine clearance. Dose adjustment based on creatinine clearance is recommended (see **DOSAGE AND ADMINISTRATION:**Monitoring and Adjusting Therapy; Use in Renal Impairment). In patients with marked renal insufficiency (creatinine clearance below 15 mL/min), and on hemodialysis, elimination half-lives are prolonged up to 2 days.
Lepirudin is thought to be metabolized by release of amino acids via catabolic hydrolysis of the parent drug. However, conclusive data are not available. About 48% of the administration dose is excreted in the urine which consists of unchanged drug (35%) and other fragments of the parent drug.
The systemic clearance of lepirudin in women is about 25% lower than in men. In elderly patients, the systemic clearance of lepirudin is 20% lower than in younger patients. This may be explained by the lower creatinine clearance in elderly patients compared to younger patients.
Table 1 summarizes systemic clearance (Cl) and volume of distribution at steady state (Vss) of lepirudin for various study populations.
Table 1: Systemic clearance (Cl) and volume of distribution at steady state (Vss) of lepirudin

	Cl (mL/min) Mean (% CV*)	Vss (L) Mean (% CV*)
Healthy young subjects (n = 18, age 18-60 years)	164 (19.3%)	12.2 (16.4%)
Healthy elderly subjects (n = 10, age 65-80 years)	139 (22.5%)	18.7 (20.6%)
Renally impaired patients (n = 16, creatinine clearance below 80 mL/min)	61 (89.4%)	18.0 (41.1%)
HIT patients (n = 73)	114 (46.8%)	32.1 (98.9%)
HAT: Heparin-associated thrombocytopenia		

***CV: Coefficient of variation**

Pharmacodynamic Properties

The pharmacodynamic effect of REFLUDAN on the proteolytic activity of thrombin was routinely assessed as an increase in aPTT. This was observed with increasing plasma concentrations of lepirudin, with no saturable effect up to the highest tested dose (0.5

mg/kg body weight intravenous bolus). Thrombin time (TT) frequently exceeded 200 seconds even at low plasma concentrations of lepirudin, which renders this test unsuitable for routine monitoring of REFLUDAN therapy.
The pharmacodynamic response defined by the aPTT ratio (aPTT at a time after REFLUDAN administration over an aPTT reference value, usually median of the laboratory normal range for aPTT) depends on plasma drug levels which in turn depend on the individual patient's renal function (see **CLINICAL PHARMACOLOGY:**Pharmacokinetic Properties). For patients undergoing additional thrombolysis, elevated aPTT ratios were already observed at low lepirudin plasma concentrations, and further response to increasing plasma concentrations was relatively flat. In other populations, the response was steeper. At plasma concentrations of 1500 ng/mL, aPTT ratios were nearly 3.0 for healthy volunteers, 2.3 for patients with heparin-associated thrombocytopenia, and 2.1 for patients with deep venous thrombosis.

CLINICAL TRIAL DATA
Heparin-induced thrombocytopenia (HIT) is described as an allergy-like adverse reaction to heparin. It can be found in about 1% to 2% of patients treated with heparin for more than 4 days. The clinical picture of HIT is characterized by thrombocytopenia alone or in combination with thromboembolic complications (TECs). These complications comprise the entire spectrum of venous and arterial thromboembolism including deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and occlusion of limb arteries, which may ultimately result in necroses requiring amputation. Furthermore, there is evidence to suggest that warfarin-induced venous limb gangrene may be associated with HIT. Without further treatment, the mortality in HIT patients with new TECs is about 20% to 30% (*Fondu 1995; Greinacher 1995; Warkentin, Chong, et al., Warkentin, Elavathil, et al. 1997*).
The conclusion that REFLUDAN is an effective treatment for HIT is based upon the data of two prospective, historically controlled clinical trials ("HAT-1" study and "HAT-2" study). The trials were comparable with regard to study design, primary and secondary objectives, and dosing regimens, as well as general study outline and organization. They both used the same historical control group for comparison. This historical control was mainly compiled from a recent retrospective registry of HIT patients.
Overall, 198 (HAT-1: 82, HAT-2: 116) patients were treated with REFLUDAN and 182 historical control patients were treated with other therapies. All except 5 (HAT-1: 1, HAT-2: 4) prospective patients and all historical control patients were diagnosed with HIT using the heparin-induced platelet activation assay (HIPAA) or equivalent assays for testing. In total, 113 (HAT-1: 54, HAT-2: 59) prospective patients ("REFLUDAN") and 91 historical control patients ("historical control") presented with TECs at baseline (day of positive test result) and qualified for direct comparison of clinical endpoints.
The gender distribution was found to be similar in REFLUDAN patients and historical control patients. Overall, REFLUDAN patients tended to be younger than historical control patients. Table 2 summarizes the demographic baseline characteristics of patients presenting with TECs at baseline.
Table 2: Demographic baseline characteristics of patients presenting with TECs

	REFLUDAN		Historical Control
	HAT –1 (n = 54)	HAT –2 (n = 59)	(n = 91)
Males	27.8%	44.1%	35.2%
Females	72.2%	55.9%	64.8%
Age <65 years	63.0%	67.8%	44.0%
Age > 65 years	37.0%	32.2%	56.0%
Mean age ± SD (years)	57 ± 17	58 ± 12	64 ± 14

The key criteria of efficacy from a laboratory standpoint (n = 115 evaluable patients) were platelet recovery (increase in platelet count by at least 30% of nadir to values >100,000) and effective anticoagulation (aPTT ratio >1.5 with a maximum total 40% increase in the initial infusion rate). The proportions of REFLUDAN patients presenting with TECs at baseline who showed platelet recovery, effective anticoagulation, or both (laboratory responders) are shown in Table 3. Comparable rates for the historical control group cannot be given, because (1) platelet counts were not monitored as closely as in the REFLUDAN group, and (2) most historical control patients did not receive therapies affecting aPTT.
Table 3: Proportions of laboratory responders among REFLUDAN patients presenting with TECs

	HAT-1	HAT-2
Number of evaluable patients	55	60
Platelet recovery	90.9%	95.0%
Effective anticoagulation	81.8%	75.0%
Both	72.7%	71.7%

Comparisons of clinical efficacy were made between REFLUDAN patients and historical control patients with regard to the combined and individual incidences of death, limb amputation, or new TEC.
The original main analyses included all events that occurred after laboratory confirmation of HIT. This approach revealed to be substantially confounded by the relative contribution of the pretreatment period (time between laboratory confirmation of HIT and

start of treatment). Although short in duration (mean length 1.5 days in HAT-1 and 2.0 days in HAT-2), the pretreatment period accounted for 45% and 26% of events observed in the main analyses of HAT-1 REFLUDAN patients and HAT-2 REFLUDAN patients, respectively.
Therefore, initiation of treatment was set as the starting point for the analyses. For the historical control group, the first treatment selected within 2 days of laboratory confirmation of HIT was used for reference.
Seven days after start of treatment, the cumulative risk of death, limb amputation, or new TEC was 3.7% in the HAT-1 REFLUDAN patients and 16.9% in the HAT-2 REFLUDAN patients, as compared to 24.9% in the historical control group. At 35 days, when approximately 10% of patients were still at risk, the cumulative risk was 13.0% in the HAT-1 REFLUDAN patients and 28.9% in the HAT-2 REFLUDAN patients, as compared to 47.8% in the historical control group.
In an additional meta-analysis, the pooled REFLUDAN patients of the HAT-1 and HAT-2 studies who presented with TECs at baseline were compared to the respective historical control patients. Seven and 35 days after start of treatment, the cumulative risks of death were 4.4% and 8.9% in the REFLUDAN group, as compared to 1.4% and 17.6% in the historical control group. The cumulative risks of limb amputation were 2.7% and 6.5% in the REFLUDAN group, as compared to 2.6% and 10.4% in the historical control group. Most importantly, the cumulative risks of new TEC were 6.3 % and 10.1% in the REFLUDAN group, as compared to 22.2% and 27.2% in the historical control group. As shown in Fig 1, differences in the cumulative risk of death, limb amputation, or new TEC between the groups were statistically significant in favor of REFLUDAN in the analysis of time to event (*P*=0.004 according to log-rank test).

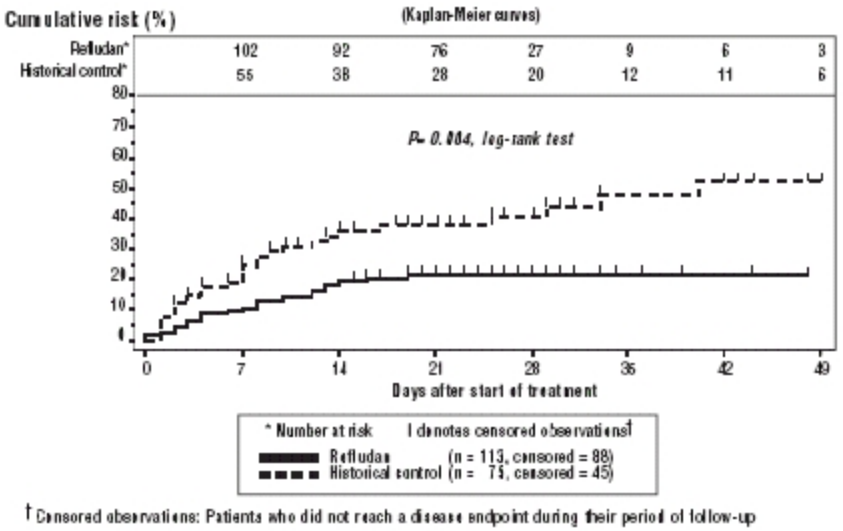

Fig 1: Cumulative risk of death, limb amputation, or new thromboembolic complication after start of treatment

The immediate impact of treatment on the combined risk of death, limb amputation, or new TEC is demonstrated by comparing pretreatment period and treatment period in regard to average combined event rates per patient day. In the pretreatment period, these rates were found to be 0.075 in the HAT-1 REFLUDAN patients, 0.052 in the HAT-2 REFLUDAN patients, and 0.040 in the historical control group. In the treatment period, the rates showed a marked reduction in the REFLUDAN patients, where they dropped to 0.005 (HAT-1) and to 0.018 (HAT-2), while there was only a moderate decrease to 0.030 in the historical control group. In conclusion, REFLUDAN substantially reduced the risk of serious sequelae of HIT in comparison to a historical control group.

INDICATIONS AND USAGE
Refludan is indicated for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications.

CONTRAINDICATIONS
REFLUDAN is contraindicated in patients with known hypersensitivity to hirudins or to any of the components in REFLUDAN [lepirudin (rDNA) for injection].

WARNINGS

Hemorrhagic Events
As with other anticoagulants, hemorrhage can occur at any site in patients receiving REFLUDAN. An unexpected fall in hemoglobin, fall in blood pressure or any unexplained symptom should lead to consideration of a hemorrhagic event. While patients are being anticoagulated with REFLUDAN, the anticoagulation status should be monitored closely using an

appropriate measure such as the aPTT (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION: Monitoring section.)
Intracranial bleeding following concomitant thrombolytic therapy with rt-PA or streptokinase may be life-threatening. There have been reports of intracranial bleeding with REFLUDAN in the absence of concomitant thrombolytic therapy (see ADVERSE REACTIONS.)
For patients with increased risk of bleeding, a careful assessment weighing the risk of REFLUDAN administration vs its anticipated benefit has to be made by the treating physician:
In particular, this includes the following conditions:

- **Recent puncture of large vessels or organ biopsy**
- **Anomaly of vessels or organs**
- **Recent cerebrovascular accident, stroke, intracerebral surgery, or other neuraxail procedures**
- **Severe uncontrolled hypertension**
- **Bacterial endocarditis**
- **Advanced renal impairment (see also WARNINGS: Renal Impairment)**
- **Hemorrhagic diathesis**
- **Recent major surgery**
- **Recent major bleeding (eg, intracranial, gastrointestinal, intraocular, or pulmonary bleeding)**
- **Recent active peptic ulcer**

Renal Impairment
With renal impairment, relative overdose might occur even with standard dosage regimen. Therefore, the bolus dose and the rate of infusion must be reduced in patients with known or suspected renal insufficiency **CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL**. (see **CLINICAL PHARMACOLOGY**: Pharmacokinetic Properties and **DOSAGE AND ADMINISTRATION**: Monitoring and Adjusting Therapy; Use in Renal Impairment).

PRECAUTIONS

General

Antibodies
Formation of antihirudin antibodies was observed in about 40% of HIT patients treated with REFLUDAN. This may increase the anticoagulant effect of REFLUDAN possibly due to delayed renal elimination of active lepirudin-antihirudin complexes (see also **PRECAUTIONS**: Animal Pharmacology and Toxicology). Therefore, strict monitoring of aPTT is necessary also during prolonged therapy (see also **PRECAUTIONS**: Laboratory tests and DOSAGE AND ADMINISTRATION: Monitoring and Adjusting Therapy; Standard Recommendations). No evidence of neutralization of REFLUDAN or of allergic reactions associated with positive antibody test results was found.

Liver Injury
Serious liver injury (eg, liver cirrhosis) may enhance the anticoagulant effect of REFLUDAN due to coagulation defects secondary to reduced generation of vitamin K-dependent coagulation factors.

Reexposure
During the HAT-1 and HAT-2 studies, a total of 13 patients were reexposed to REFLUDAN. One of these patients experienced a mild allergic skin reaction during the second treatment cycle. In post marketing experience, anaphylaxis after reexposure has been reported. (see **PRECAUTIONS—Allergic Reactions** below and **ADVERSE REACTIONS—Adverse Events from Post Marketing Reports.**)

Allergic Reactions
There have been reports of allergic and hypersensitivity reactions including anaphylactic reactions. Serious anaphylactic reactions that have resulted in shock or death have been reported. These reactions have been reported during initial administration or upon second or subsequent reexposure(s).

Laboratory tests
In general, the dosage (infusion rate) should be adjusted according to the aPTT ratio (patient aPTT at a given time over an aPTT reference value, usually median of the laboratory normal range for aPTT); for full information, see **DOSAGE AND ADMINISTRATION**: Monitoring and Adjusting Therapy; Standard Recommendations. Other thrombin-dependent coagulation assays are changed by REFLUDAN (see also DESCRIPTION).

Drug interactions
Concomitant treatment with thrombolytics (eg, rt-PA or streptokinase) may
- increase the risk of bleeding complications

- considerably enhance the effect of REFLUDAN on aPTT prolongation.

(See also **WARNINGS**: Hemorrhagic Events, ADVERSE REACTIONS: Adverse Events Reported in Other Populations; Intracranial Bleeding and **DOSAGE AND ADMINISTRATION**: Monitoring and Adjusting Therapy; Concomitant Use With Thrombolytic Therapy.)
Concomitant treatment with coumarin derivatives (vitamin K antagonists) and drugs that affect platelet function may also increase the risk of bleeding (see also DOSAGE AND ADMINISTRATION: Monitoring and Adjusting Therapy; Use in Patients Scheduled for a Switch to Oral Anticoagulation).

Animal Pharmacology and Toxicology

General Toxicity
Lepirudin caused bleeding in animal toxicity studies. Antibodies against hirudin which appeared in several monkeys treated with lepirudin resulted in a prolongation of the terminal half-life and an increase of AUC plasma values of lepirudin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the potential for carcinogenesis have not been performed with lepirudin. Lepirudin was not genotoxic in the Ames test, the Chinese hamster cell (V79/HGPRT) forward mutation test, the A549 human cell line unscheduled DNA synthesis (UDS) test, the Chinese hamster V79 cell chromosome aberration test, or the mouse micronucleus test. An effect on fertility and reproductive performance of male and female rats was not seen with lepirudin at intravenous doses up to 30 mg/kg/day (180 mg/m^2/day, 1.2 times the recommended maximum human total daily dose based on body surface area of 1.45m^2 for a 50 kg subject).

Pregnancy

Teratogenic Effects: Category B

Teratology studies with lepirudin performed in pregnant rats at intravenous doses up to 30 mg/kg/day (180 mg/m^2/day, 1.2 times the recommended maximum human total daily dose based on body surface area) and in pregnant rabbits at intravenous doses up to 30 mg/kg/day (360 mg/m^2/day, 2.4 times the recommended maximum human total daily dose based on body surface area) have revealed no evidence of harm to the fetus due to lepirudin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lepirudin (1 mg/kg) by intravenous administration crosses the placental barrier in pregnant rats. It is not known whether the drug crosses the placental barrier in humans.

Following intravenous administration of lepirudin at 30 mg/kg/day (180 mg/m^2/day, 1.2 times the recommended maximum human total daily dose based on body surface area) during organogenesis and perinatal-postnatal periods, pregnant rats showed an increased maternal mortality due to undetermined causes.

Nursing Mothers
It is not known whether REFLUDAN is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from REFLUDAN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. In the HAT-2 study, two children, an 11-year-old girl and a 12-year-old boy, were treated with REFLUDAN. Both children presented with TECs at baseline. REFLUDAN doses given ranged from 0.15 mg/kg/h to 0.22 mg/kg/h for the girl, and from 0.1 mg/kg/h (in conjunction with urokinase) to 0.7 mg/kg/h for the boy. Treatment with REFLUDAN was completed after 8 and 58 days, respectively, without serious adverse events *(Schiffmann 1997)*.

ADVERSE REACTIONS

Adverse Events Reported in Clinical Trials in HIT Patients

The following safety information is based on all 198 patients treated with REFLUDAN in the HAT-1 and HAT-2 studies. The safety profile of 113 REFLUDAN patients from these studies who presented with TECs at baseline is compared to 91 such patients in the historical control.

Hemorrhagic Events

Bleeding was the most frequent adverse event observed in patients treated with REFLUDAN. Table 4 gives an overview of all hemorrhagic events which occurred in at least two patients.

Table 4: Hemorrhagic Events*

	HAT-1 HAT-2 **(All patients)** **(n = 198)**	Patients with TECs	
		REFLUDAN **(n = 113)**	**Historical control** **(n = 91)**
Bleeding from puncture sites and wounds	**14.1%**	**10.6%**	**4.4%**
Anemia or isolated drop in hemoglobin	**13.1%**	**12.4%**	**1.1%**
Other hematoma and unclassified bleeding	**11.1%**	**10.6%**	**4.4%**
Hematuria	**6.6%**	**4.4%**	**0**
Gastrointestinal and rectal bleeding	**5.1%**	**5.3%**	**6.6%**
Epistaxis	**3.0%**	**4.4%**	**1.1%**
Hemothorax	**3.0%**	**0**	**1.1%**
Vaginal bleeding	**1.5%**	**1.8%**	**0**
Intracranial bleeding	**0**	**0**	**2.2%**

***Patients may have suffered more than one event

Other hemorrhagic events (hemoperitoneum, hemoptysis, liver bleeding, lung bleeding, mouth bleeding, retroperitoneal bleeding) each occurred in one individual among all 198 patients treated with REFLUDAN.

Nonhemorrhagic events

Table 5 gives an overview of the most frequently observed nonhemorrhagic events.

Table 5: Nonhemorrhagic adverse events*

	HAT-1 **HAT-2** **(All patients)** **(n = 198)**	Patients with TECs	
		REFLUDAN **(n = 113)**	**Historical control** **(n = 91)**
Fever	**6.1%**	**4.4%**	**8.8%**
Abnormal liver function	**6.1%**	**5.3%**	**0**
Pneumonia	**4.0%**	**4.4%**	**5.5%**

Sepsis	**4.0%**	**3.5%**	**5.5%**
Allergic skin reactions	**3.0%**	**3.5%**	**1.1%**
Heart failure	**3.0%**	**1.8%**	**2.2%**
Abnormal kidney function	**2.5%**	**1.8%**	**4.4%**
Unspecified infections	**2.5%**	**1.8%**	**1.1%**
Multiorgan failure	**2.0%**	**3.5%**	**0**
Pericardial effusion	**1.0%**	**0**	**1.1%**
Ventricular fibrillation	**1.0%**	**0**	**0**

*****Patients may have suffered more than one event

Adverse Events Reported in Clinical Trials in Other Populations
The following safety information is based on a total of 2302 individuals who were treated with REFLUDAN in clinical pharmacology studies (n = 323) or for clinical indications other than HIT (n = 1979).

Intracranial Bleeding
Intracranial bleeding was the most serious adverse reaction found in populations other than HIT patients. It occurred in patients with acute myocardial infarction who were started on both REFLUDAN and thrombolytic therapy with rt-PA or streptokinase. The overall frequency of this potentially life-threatening complication among patients receiving both REFLUDAN and thrombolytic therapy was 0.6% (7 out of 1134 patients). Although no intracranial bleeding was observed in 1168 subjects or patients who did not receive concomitant thrombolysis, there have been post marketing reports of intracranial bleeding with REFLUDAN in the absence of concomitant thrombolytic therapy (see**ADVERSE REACTIONS—Adverse Events from Post Marketing Reports** and **WARNINGS**.)

Allergic Reactions
(See **PRECAUTIONS.**)

Allergic reactions or suspected allergic reactions in populations other than HIT patients include (in descending order of frequency*):

Airway reactions (cough, bronchospasm, stridor, dyspnea):	common
Unspecified allergic reactions:	uncommon
Skin reactions (pruritus, urticaria, rash, flushes, chills):	uncommon
General reactions (anaphylactoid or anaphylactic reactions):	uncommon
Edema (facial edema, tongue edema, larynx edema, angioedema):	rare

* The CIOMS (Council for International Organization of Medical Sciences) III standard categories are used for classification of frequencies:

very common	10% or more
common (frequent)	1 to <10%
uncommon (infrequent)	0.1 to<1%
rare	0.01 to <0.1%
very rare	0.01% or less

About 53% (n = 46) of all allergic reactions or suspected allergic reactions occurred in patients who concomitantly received thrombolytic therapy (eg, streptokinase) for acute myocardial infarction and/or contrast media for coronary angiography.

Adverse Events from Post Marketing Reports
Serious anaphylactic reactions that have resulted in shock or death have been reported. (See **PRECAUTIONS**.)
Intracranial bleeding has been reported in patients treated with REFLUDAN with or without concomitant thrombolytic therapy. (SeeWARNINGS.) Although no intracranial bleeding was observed in Clinical Trials in those patients who did not receive concomitant thrombolytic therapy (see **Adverse Events Reported in Clinical Trials in HIT Patients** and **Adverse Events Reported in Clinical Trials in Other Populations** below), there have been post marketing reports of intracranial bleeding in patients who received REFLUDAN without concomitant thrombolytic therapy.

OVERDOSAGE
In case of overdose (eg, suggested by excessively high aPTT values) the risk of bleeding is increased.

No specific antidote for REFLUDAN is available. If life-threatening bleeding occurs and excessive plasma levels of lepirudin are suspected, the following steps should be followed:

- Immediately STOP REFLUDAN administration
- Determine aPTT and other coagulation levels as appropriate
- Determine hemoglobin and prepare for blood transfusion
- Follow the current guidelines for treating patients with shock

Individual clinical case reports and in vitro data suggest that either hemofiltration or hemodialysis (using high-flux dialysis membranes with a cutoff point of 50,000 daltons, eg, AN/69) may be useful in this situation.
In studies in pigs, the application of von Willebrand Factor (vWF, 66 IU/kg body weight) markedly reduced the bleeding time. The clinical significance of this data is unknown.

DOSAGE AND ADMINISTRATION

Initial Dosage

Anticoagulation in adult patients with HIT and associated thromboembolic disease:

- 0.4 mg/kg body weight (up to 110 kg) slowly intravenously (eg, over 15 to 20 seconds) as a bolus dose. **CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL**.
- followed by 0.15 mg/kg body weight (up to 110 kg)/hour as a continuous intravenous infusion for 2 to 10 days or longer if clinically needed.

Normally the initial dosage depends on the patient's body weight. This is valid up to a body weight of 110 kg. In patients with a body weight exceeding 110 kg, the initial dosage should not be increased beyond the 110 kg body weight dose (maximal initial bolus dose of 44 mg, maximal initial infusion dose of 16.5 mg/h; see also **DOSAGE AND ADMINISTRATION**: Administration; Initial Intravenous Bolus, Table 7 and **DOSAGE AND ADMINISTRATION**: Administration; Intravenous Infusion, Table 8).
In general, therapy with REFLUDAN is monitored using the aPTT ratio (patient aPTT at a given time over an aPTT reference value, usually median of the laboratory normal range for aPTT, see **DOSAGE AND ADMINISTRATION**: Monitoring and Adjusting Therapy; Standard Recommendations). A patient baseline aPTT should be determined prior to initiation of therapy with REFLUDAN, since REFLUDAN should not be started in patients presenting with a baseline aPTT ratio of 2.5 or more, in order to avoid initial overdosing.

Monitoring and Adjusting Therapy
Standard Recommendations.

Monitoring

- **In general, the dosage (infusion rate) should be adjusted according to the aPTT ratio (patient aPTT at a given time over an aPTT reference value, usually median of the laboratory normal range for aPTT).**
- **The target range for the aPTT ratio during treatment (therapeutic window) should be 1.5 to 2.5. Data from clinical trials in HIT patients suggest that with aPTT ratios higher than this target range, the risk of bleeding increases, while there is no incremental increase in clinical efficacy.**
- **As stated in DOSAGE AND ADMINISTRATION: Initial Dosage, REFLUDAN should not be started in patients presenting with a baseline aPTT ratio of 2.5 or more, in order to avoid initial overdosing.**
- **The first aPTT determination for monitoring treatment should be done 4 hours after start of the REFLUDAN infusion.**
- **Follow-up aPTT determinations are recommended at least once daily, as long as treatment with REFLUDAN is ongoing.**
- **More frequent aPTT monitoring is highly recommended in patients with renal impairment or serious liver injury (see DOSAGE AND ADMINISTRATION: Monitoring and Adjusting Therapy; Use in Renal Impairment) or with an increased risk of bleeding.**

Dose Modifications

- **Any aPTT ratio out of the target range is to be confirmed at once before drawing conclusions with respect to dose modifications, unless there is a clinical need to react immediately.**

- **If the confirmed aPTT ratio is above the target range, the infusion should be stopped for two hours. At restart, the infusion rate should be decreased by 50% (no additional intravenous bolus should be administered). The aPTT ratio should be determined again 4 hours later.**

- I**f the confirmed aPTT ratio is below the target range, the infusion rate should be increased in steps of 20%. The aPTT ratio should be determined again 4 hours later.**

- **In general, an infusion rate of 0.21 mg/kg/h should not be exceeded without checking for coagulation abnormalities which might be preventive of an appropriate aPTT response.**

Use in Renal Impairment

As REFLUDAN is almost exclusively excreted in the kidneys (see also CLINICAL PHARMACOLOGY: Pharmacokinetic Properties), individual renal function should be considered prior to administration. In case of renal impairment, relative overdose might occur even with the standard dosage regimen. Therefore, the bolus dose and the infusion rate must be reduced in case of known or suspected renal insufficiency (creatinine clearance below 60 mL/min or serum creatinine above 1.5 mg/dL). **CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL**. There is only limited information on the therapeutic use of REFLUDAN in HIT patients with significant renal impairment. The following dosage recommendations are mainly based on single-dose studies in a small number of patients with renal impairment.

Therefore, these recommendations are only tentative and aPTT monitoring should be used along with monitoring of renal status. Dose adjustments should be based on creatinine clearance values, whenever available, as obtained from a reliable method (24 h urine sampling). If creatinine clearance is not available, the dose adjustments should be based on the serum creatinine.

In all patients with renal insufficiency, the bolus dose is to be reduced to 0.2 mg/kg body weight. **CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL**.

The standard initial infusion rate given in **DOSAGE AND ADMINISTRATION**: Initial Dosage and DOSAGE AND ADMINISTRATION: Administration; Intravenous Infusion, Table 8 must be reduced according to the recommendations given in Table 6. Additional aPTT monitoring is highly recommended.

Table 6: Reduction of infusion rate in patients with renal impairment

Creatinine clearance [mL/min]	Serum creatinine [mg/dL]	Adjusted infusion rate	
		[% of standard initial infusion rate]	[mg/kg/h]
45 – 60	1.6 - 2.0	50%	0.075
30 – 44	2.1 - 3.0	30%	0.045
15 – 29	3.1 - 6.0	15%	0.0225
below 15*	above 6.0*	avoid or STOP infusion!*	

*****In hemodialysis patients or in case of acute renal failure (creatinine clearance below 15 mL/min or serum creatinine above 6.0 mg/dL), infusion of REFLUDAN is to be avoided or stopped. Additional intravenous bolus doses of 0.1 mg/kg body weight should be considered every other day only if the aPTT ratio falls below the lower therapeutic limit of 1.5. **CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL**. (see also DOSAGE AND ADMINISTRATION: Monitoring and Adjusting Therapy; Standard Recommendations).

Concomitant Use With Thrombolytic Therapy

Clinical trials in HIT patients have provided only limited information on the combined use of REFLUDAN and thrombolytic agents. The following dosage regimen of REFLUDAN was used in a total of 9 HIT patients in the HAT-1 and HAT-2 studies who presented with TECs at baseline and were started on both REFLUDAN and thrombolytic therapy (rt-PA, urokinase or streptokinase):

- Initial intravenous bolus: 0.2 mg/kg body weight. **CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL**

- Continuous intravenous infusion: 0.1 mg/kg body weight/h

The number of patients receiving combined therapy was too small to identify differences in clinical outcome of patients who were started on both REFLUDAN and thrombolytic therapy as compared to those who were started on REFLUDAN alone. The combined incidences of death, limb amputation, or new TEC were 22.2% and 20.7%, respectively. While there was a 47% relative increase in the overall bleeding rate in patients who were started on both REFLUDAN and thrombolytic therapy (55.6% vs. 37.9%), there were no differences in the rates of serious bleeding events (fatal or life-threatening bleeds, bleeds that were permanently or significantly disabling, overt bleeds requiring transfusion of 2 or more units of packed red blood cells, bleeds necessitating surgical intervention, intracranial bleeds) between the groups (11.1% vs. 11.2%). Although no intracranial bleeding has been observed in any of these patients, there have been reports of intracranial bleeding in the presence or absence of concomitant thrombolytic therapy. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Special attention should be paid to the fact that thrombolytic agents per se may increase the aPTT ratio. Therefore, aPTT ratios with a given plasma level of lepirudin are usually higher in patients who receive concomitant thrombolysis than in those who do not (see also **CLINICAL PHARMACOLOGY**: Pharmacodynamic Properties).

Use in Patients Scheduled for a Switch to Oral Anticoagulation
In the absence of other anticoagulants, REFLUDAN influences the INR/prothrombin time in a dose dependent, gradual and linear fashion when aPTT values are within the recommended therapeutic range.
In REFLUDAN-treated patients receiving overlapping therapy with oral anticoagulants, there may be a small reduction in INR upon cessation of REFLUDAN treatment. When transitioning from REFLUDAN to oral anticoagulation, PT/INR should be monitored closely until results stabilize in the therapeutic range.
If a patient is scheduled to receive coumarin derivatives (vitamin K antagonists) for oral anticoagulation after REFLUDAN therapy, the dose of REFLUDAN should first be gradually reduced in order to reach an aPTT ratio just above 1.5 before initiating oral anticoagulation. Coumarin derivatives should be initiated only when platelet counts are normalizing. The intended maintenance dose should be started with no loading dose. To avoid prothrombotic effects when initiating coumarin, continue parenteral anticoagulation for 4 to 5 days (see oral anticoagulant package insert for information.) The parenteral agent can be discontinued when the INR stabilizes within the desired target range.

Administration

Directions on Preparation and Dilution
REFLUDAN should not be mixed with other drugs except for Sterile Water for Injection USP, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection.

Use REFLUDAN before the expiration date given on the carton and container.

Reconstitution and further dilution are to be carried out under sterile conditions:

- For reconstitution, Sterile Water for Injection USP or 0.9% Sodium Chloride Injection USP are to be used.
- For further dilution, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection are suitable.
- For rapid, complete reconstitution, inject 1 mL of diluent into the vial and shake it gently. After reconstitution a clear, colorless solution is usually obtained in a few seconds, but definitely in less than 3 minutes. **CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL.**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use solutions that are cloudy or contain particles.
- The reconstituted solution is to be used immediately. It remains stable for up to 24 hours at room temperature (eg, during infusion).
- The preparation should be warmed to room temperature before administration.
- Discard any unused solution appropriately.

Initial Intravenous Bolus
CAUTION: Preparation of a Refludan bolus injection requires dilution following reconstitution in order to obtain the final concentration of 5 mg/mL.

For intravenous bolus injection, use a solution with a concentration of 5 mg/mL.

Preparation of a REFLUDAN solution with a concentration of 5 mg/mL:

- Reconstitute one vial (50 mg of lepirudin) with 1 mL of Sterile Water for Injection USP or 0.9% Sodium Chloride Injection USP. **Reconstitution with 1 mL of diluent results in a concentration of 50 mg/mL. Once reconstituted, this product must be further diluted prior to administration.**
- The final concentration of 5 mg/mL is obtained by transferring the contents of the vial into a sterile, single-use syringe (of at least 10 mL capacity) and diluting the solution to a total volume of 10 mL, using Sterile Water for injection USP, 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection.
- The final solution is to be administered according to body weight (see Table 7 below and **DOSAGE AND ADMINISTRATION**: Initial Dosage).

• Intravenous injection of the bolus is to be carried out slowly (eg, over 15 to 20 seconds).

Table 7: Standard bolus injection volumes according to body weight for a 5 mg/mL concentration

Body Weight [kg]	Injection volume	
	Dosage 0.4 mg/kg	Dosage 0.2 mg/kg*
50	4.0 mL	2.0 mL
60	4.8 mL	2.4 mL
70	5.6 mL	2.8 mL
80	6.4 mL	3.2 mL
90	7.2 mL	3.6 mL
100	8.0 mL	4.0 mL
110	8.8 mL	4.4 mL

*****Dosage recommended for all patients with renal insufficiency (see **DOSAGE AND ADMINISTRATION**: **Monitoring and Adjusting Therapy; Use in Renal Impairment).**

Intravenous Infusion
For continuous intravenous infusion, solutions with concentration of 0.2 mg/mL or 0.4 mg/mL may be used.

Preparation of a REFLUDAN solution with a concentration of 0.2 or 0.4 mg/mL:

• Reconstitute two vials (each containing 50 mg of lepirudin) with 1 mL each using either Sterile Water for Injection USP or 0.9% Sodium Chloride Injection USP.

• The final concentrations of 0.2 mg/mL or 0.4 mg/mL are obtained by transferring the contents of both vials into an infusion bag containing 500 mL or 250 mL of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection.

The infusion rate [mL/h] is to be set according to body weight (see Table 8 below and DOSAGE AND ADMINISTRATION: Initial Dosage).

Table 8: Standard infusion rates according to body weight

Body Weight [kg]	Infusion rate at 0.15 mg/kg/h	
	500-mL infusion bag 0.2 mg/mL	250-mL infusion bag 0.4 mg/mL
50	38 mL/h	19 mL/h
60	45 mL/h	23 mL/h
70	53 mL/h	26 mL/h
80	60 mL/h	30 mL/h
90	68 mL/h	34 mL/h
100	75 mL/h	38 mL/h
110	83 mL/h	41 mL/h

HOW SUPPLIED
REFLUDAN [lepirudin (rDNA) for injection] is supplied in boxes of 10 vials, each vial containing 50 mg lepirudin (NDC 50419-150-57). STORE UNOPENED VIALS AT 2 TO 25°C (35.6 TO 77°F). USE REFLUDAN BEFORE THE EXPIRATION DATE GIVEN ON THE CARTON AND CONTAINER. ONCE RECONSTITUTED, USE REFLUDAN IMMEDIATELY.

REFERENCES
1. Fondu P. Heparin associated thrombocytopenia: an update. *Acta Clinica Belgica. 1995; 50-6:343-357.*

2. Greinacher A. Antigen generation in heparin-associated thrombocytopenia: the non-immunologic type and the immunologic type are closely linked in their pathogenesis. *Seminars Thromb Hemost. 1995; 2l:106-116*.

3. Roethig HJ, Maree JS, Meyer BH. Clinical pharmacology of hirudin (HBW 023). In: Reidenberg, MM ed. *The clinical pharmacology of biotechnology products*. Elsevier Publishers; 1991:227-236.

4. Schiffmann H. Unterhalt M, Harms K, Figula HR, Voelpel H, Greinacher A. Successful treatment of heparin-induced thrombocytopenia (HIT) type II in childhood with recombinant hirudin. *Monatsschr Kinderheilkd*. 1997; 145:606-612.

5. Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards consensus. *Thromb Haemostas*. In Press.

6. Warkentin TE, Elavathil LJ, Hayward CPM, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med. 1997; 127:804-812*.

Prescribing Information as of December 2006
Manufactured by: CSL Behring GmbH D-35002 Marburg Germany
Manufactured for:
Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470
Made in Germany www.refludan.com
64011246
6701500 US